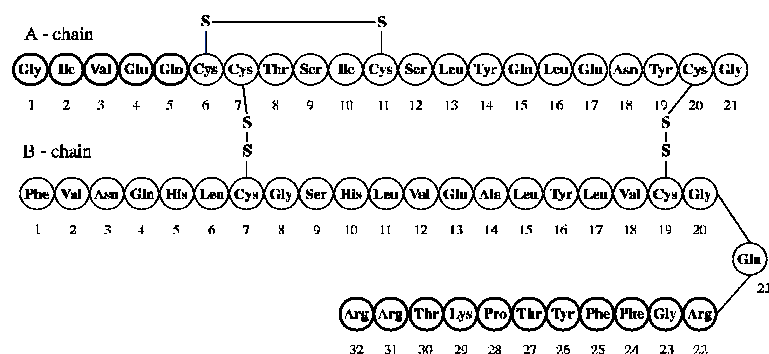


Rev. XXX

Rx Only**LANTUS[®]****(insulin glargine [rDNA origin] injection)****LANTUS[®] must NOT be diluted or mixed with any other insulin or solution.****DESCRIPTION**

LANTUS[®] (insulin glargine [rDNA origin] injection) is a sterile solution of insulin glargine for use as an injection. Insulin glargine is a recombinant human insulin analog that is a long-acting (up to 24-hour duration of action), parenteral blood-glucose-lowering agent. (See CLINICAL PHARMACOLOGY). LANTUS is produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of *Escherichia coli* (K12) as the production organism. Insulin glargine differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and two arginines are added to the C-terminus of the B-chain. Chemically, it is 21^A-Gly-30^Ba-L-Arg-30^Bb-L-Arg-human insulin and has the empirical formula C₂₆₇H₄₀₄N₇₂O₇₈S₆ and a molecular weight of 6063. It has the following structural formula:



LANTUS consists of insulin glargine dissolved in a clear aqueous fluid. Each milliliter of LANTUS (insulin glargine injection) contains 100 IU (3.6378 mg) insulin glargine, 30 mcg zinc, 2.7 mg m-cresol, 20 mg glycerol 85%, and water for injection. The pH is adjusted by addition of aqueous solutions of hydrochloric acid and sodium hydroxide. LANTUS has a pH of approximately 4.

CLINICAL PHARMACOLOGY

Mechanism of Action:

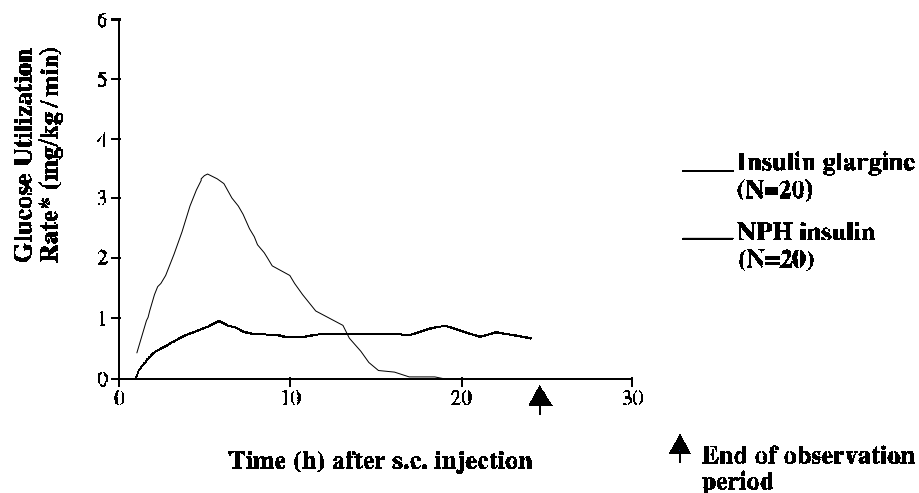
The primary activity of insulin, including insulin glargine, is regulation of glucose metabolism. Insulin and its analogs lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis, and enhances protein synthesis.

Pharmacodynamics:

Insulin glargine is a human insulin analog that has been designed to have low aqueous solubility at neutral pH. At pH 4, as in the LANTUS injection solution, it is completely soluble. After injection into the subcutaneous tissue, the acidic solution is neutralized, leading to formation of microprecipitates from which small amounts of insulin glargine are slowly released, resulting in a relatively constant concentration/time profile over 24 hours with no pronounced peak. This profile allows once-daily dosing as a patient's basal insulin.

In clinical studies, the glucose-lowering effect on a molar basis (i.e., when given at the same doses) of intravenous insulin glargine is approximately the same as human insulin. In euglycemic clamp studies in healthy subjects or in patients with type 1 diabetes, the onset of action of subcutaneous insulin glargine was slower than NPH human insulin. The effect profile of insulin glargine was relatively constant with no pronounced peak and the duration of its effect was prolonged compared to NPH human insulin. *Figure 1* shows results from a study in patients with type 1 diabetes conducted for a maximum of 24 hours after the injection. The median time between injection and the end of pharmacological effect was 14.5 hours (range: 9.5 to 19.3 hours) for NPH human insulin, and 24 hours (range: 10.8 to >24.0 hours) (24 hours was the end of the observation period) for insulin glargine.

Figure 1. Activity Profile in Patients with Type 1 Diabetes[†]



* Determined as amount of glucose infused to maintain constant plasma glucose levels (hourly mean values); indicative of insulin activity.

[†] Between-patient variability (CV, coefficient of variation); insulin glargine, 84% and NPH, 78%.

The longer duration of action (up to 24 hours) of LANTUS is directly related to its slower rate of absorption and supports once-daily subcutaneous administration. The time course of action of insulins, including LANTUS, may vary between individuals and/or within the same individual.

Pharmacokinetics:

Absorption and Bioavailability. After subcutaneous injection of insulin glargine in healthy subjects and in patients with diabetes, the insulin serum concentrations indicated a slower, more prolonged absorption and a relatively constant concentration/time profile over

24 hours with no pronounced peak in comparison to NPH human insulin. Serum insulin concentrations were thus consistent with the time profile of the pharmacodynamic activity of insulin glargine.

After subcutaneous injection of 0.3 IU/kg insulin glargine in patients with type 1 diabetes, a relatively constant concentration/time profile has been demonstrated. The duration of action after abdominal, deltoid, or thigh subcutaneous administration was similar.

Metabolism. A metabolism study in humans indicates that insulin glargine is partly metabolized at the carboxyl terminus of the B chain in the subcutaneous depot to form two active metabolites with in vitro activity similar to that of insulin, M1 (21^A-Gly-insulin) and M2 (21^A-Gly-des-30^B-Thr-insulin). Unchanged drug and these degradation products are also present in the circulation.

Special Populations

Age, Race, and Gender. Information on the effect of age, race, and gender on the pharmacokinetics of LANTUS is not available. However, in controlled clinical trials in adults (n=3890) and a controlled clinical trial in pediatric patients (n=349), subgroup analyses based on age, race, and gender did not show differences in safety and efficacy between insulin glargine and NPH human insulin.

Smoking. The effect of smoking on the pharmacokinetics/pharmacodynamics of LANTUS has not been studied.

Pregnancy. The effect of pregnancy on the pharmacokinetics and pharmacodynamics of LANTUS has not been studied (see PRECAUTIONS, Pregnancy).

Obesity. In controlled clinical trials, which included patients with Body Mass Index (BMI) up to and including 49.6 kg/m², subgroup analyses based on BMI did not show any differences in safety and efficacy between insulin glargine and NPH human insulin.

Renal Impairment. The effect of renal impairment on the pharmacokinetics of LANTUS has not been studied. However, some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. Careful glucose monitoring and dose adjustments of insulin, including LANTUS, may be necessary in patients with renal dysfunction (see PRECAUTIONS, Renal Impairment).

Hepatic Impairment. The effect of hepatic impairment on the pharmacokinetics of LANTUS has not been studied. However, some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. Careful glucose monitoring and dose adjustments of insulin, including LANTUS, may be necessary in patients with hepatic dysfunction (see PRECAUTIONS, Hepatic Impairment).

CLINICAL STUDIES

The safety and effectiveness of insulin glargine given once daily at bedtime was compared to that of once-daily and twice-daily NPH human insulin in open-label, randomized, active-control, parallel studies of 2327 adult patients and 349 pediatric patients with type 1 diabetes mellitus and 1563 adult patients with type 2 diabetes mellitus (see Tables 1-3). In general, the reduction in glycated hemoglobin (HbA1c) with LANTUS was similar to that with NPH human insulin. The overall rates of hypoglycemia did not differ between patients treated with LANTUS compared to NPH human insulin.

Type 1 Diabetes–Adult (see Table 1). In two large, randomized, controlled clinical studies (Studies A and B), patients with type 1 diabetes (Study A; n=585, Study B; n=534) were randomized to basal-bolus treatment with LANTUS once daily at bedtime or to NPH human insulin once or twice daily and treated for 28 weeks. Regular human insulin was administered before each meal. LANTUS was administered at bedtime. NPH human insulin was administered once daily at bedtime or in the morning and at bedtime when used twice daily. In one large, randomized, controlled clinical study (Study C), patients with type 1 diabetes (n=619) were treated for 16 weeks with a basal-bolus insulin regimen where insulin lispro was used before each meal. LANTUS was administered once daily at bedtime and NPH human insulin was administered once or twice daily. In these studies, LANTUS and NPH human insulin had a similar effect on glycohemoglobin with a similar overall rate of hypoglycemia.

Table 1: Type 1 Diabetes Mellitus–Adult

	<u>Study A</u>		<u>Study B</u>		<u>Study C</u>	
Treatment duration	28 weeks		28 weeks		16 weeks	
Treatment in combination with	Regular insulin		Regular insulin		Insulin lispro	
	<u>LANTUS</u>	<u>NPH</u>	<u>LANTUS</u>	<u>NPH</u>	<u>LANTUS</u>	<u>NPH</u>
Number of subjects treated	292	293	264	270	310	309
HbA1c						
Endstudy mean	8.13	8.07	7.55	7.49	7.53	7.60
Adj. mean change from baseline	+0.21	+0.10	-0.16	-0.21	-0.07	-0.08
LANTUS – NPH		+0.11		+0.05		+0.01
95% CI for Treatment difference		(-0.03; +0.24)		(-0.08; +0.19)		(-0.11; +0.13)
Basal insulin dose						
Endstudy mean	19.2	22.8	24.8	31.3	23.9	29.2
Mean change from baseline	-1.7	-0.3	-4.1	+1.8	-4.5	+0.9
Total insulin dose						
Endstudy mean	46.7	51.7	50.3	54.8	47.4	50.7
Mean change from baseline	-1.1	-0.1	+0.3	+3.7	-2.9	+0.3
Fasting blood glucose (mg/dL)						
Endstudy mean	146.3	150.8	147.8	154.4	144.4	161.3
Adj. mean change from baseline	-21.1	-16.0	-20.2	-16.9	-29.3	-11.9

Type 1 Diabetes–Pediatric (see Table 2). In a randomized, controlled clinical study (Study D), pediatric patients (age range 6 to 15 years) with type 1 diabetes (n=349) were treated for 28 weeks with a basal-bolus insulin regimen where regular human insulin was used before each meal. LANTUS was administered once daily at bedtime and NPH human insulin was administered once or twice daily. Similar effects on glycohemoglobin and the incidence of hypoglycemia were observed in both treatment groups.

Table 2: Type 1 Diabetes Mellitus–Pediatric

	<u>Study D</u>	
	28 weeks	
Treatment duration	Regular insulin	
Treatment in combination with	<u>LANTUS</u>	<u>NPH</u>
Number of subjects treated	174	175
HbA1c		
Endstudy mean	8.91	9.18
Adj. mean change from baseline	+0.28	+0.27
LANTUS – NPH	+0.01	
95% CI for Treatment difference	(-0.24; +0.26)	
Basal insulin dose		
Endstudy mean	18.2	21.1
Mean change from baseline	-1.3	+2.4
Total insulin dose		
Endstudy mean	45.0	46.0
Mean change from baseline	+1.9	+3.4
Fasting blood glucose (mg/dL)		
Endstudy mean	171.9	182.7
Adj. mean change from baseline	-23.2	-12.2

Type 2 Diabetes–Adult (see Table 3). In a large, randomized, controlled clinical study (Study E) (n=570), LANTUS was evaluated for 52 weeks as part of a regimen of combination therapy with insulin and oral antidiabetes agents (a sulfonylurea, metformin, acarbose, or combinations of these drugs). LANTUS administered once daily at bedtime was as effective as NPH human insulin administered once daily at bedtime in reducing glycohemoglobin and fasting glucose. There was a low rate of hypoglycemia that was similar in LANTUS and NPH human insulin treated patients. In a large, randomized, controlled clinical study (Study F), in patients with type 2 diabetes not using oral antidiabetes agents (n=518), a basal-bolus regimen of LANTUS once daily at bedtime or NPH human insulin administered once or twice daily was evaluated for 28 weeks. Regular human insulin was used before meals as needed. LANTUS had similar effectiveness as either once- or twice-daily NPH human insulin in reducing glycohemoglobin and fasting glucose with a similar incidence of hypoglycemia.

Table 3: Type 2 Diabetes Mellitus–Adult

	<u>Study E</u>		<u>Study F</u>	
Treatment duration	52 weeks		28 weeks	
Treatment in combination with	Oral agents		Regular insulin	
	<u>LANTUS</u>	<u>NPH</u>	<u>LANTUS</u>	<u>NPH</u>
Number of subjects treated	289	281	259	259
HbA1c				
Endstudy mean	8.51	8.47	8.14	7.96
Adj. mean change from baseline	-0.46	-0.38	-0.41	-0.59
LANTUS – NPH		-0.08		+0.17
95% CI for Treatment difference		(-0.28; +0.12)		(-0.00; +0.35)
Basal insulin dose				
Endstudy mean	25.9	23.6	42.9	52.5
Mean change from baseline	+11.5	+9.0	-1.2	+7.0
Total insulin dose				
Endstudy mean	25.9	23.6	74.3	80.0
Mean change from baseline	+11.5	+9.0	+10.0	+13.1
Fasting blood glucose (mg/dL)				
Endstudy mean	126.9	129.4	141.5	144.5
Adj. mean change from baseline	-49.0	-46.3	-23.8	-21.6

LANTUS Flexible Daily Dosing

The safety and efficacy of LANTUS administered pre-breakfast, pre-dinner, or at bedtime were evaluated in a large, randomized, controlled clinical study, in patients with type 1 diabetes (study G, n=378). Patients were also treated with insulin lispro at mealtime. LANTUS administered at different times of the day resulted in similar reductions in glycated hemoglobin compared to that with bedtime administration (See Table 4). In these patients, data are available from 8-point home glucose monitoring. The maximum mean blood glucose level was observed just prior to injection of LANTUS regardless of time of administration, i.e. pre-breakfast, pre-dinner, or bedtime.

In this study, 5% of patients in the LANTUS-breakfast arm discontinued treatment because of lack of efficacy. No patients in the other two arms discontinued for this reason. Routine monitoring during this trial revealed the following mean changes in systolic blood pressure: pre-breakfast group, 1.9 mm Hg; pre-dinner group, 0.7 mm Hg; pre-bedtime group, -2.0 mm Hg.

The safety and efficacy of LANTUS administered pre-breakfast or at bedtime were also evaluated in a large, randomized, active-controlled clinical study (Study H, n=697) in type 2 diabetes patients no longer adequately controlled on oral agent therapy. All patients in this study also received AMARYL® (glimeperide) 3 mg daily. LANTUS given before breakfast was at least as effective in lowering glycated hemoglobin A_{1c} (HbA_{1c}) as LANTUS given at bedtime or NPH human insulin given at bedtime (See Table 4).

Table 4: Flexible LANTUS Daily Dosing in Type 1 (Study G) and Type 2 (Study H) Diabetes Mellitus

Treatment duration Treatment in combination with:	Study G 24 weeks			Study H 24 weeks		
	Insulin lispro			AMARYL® (glimeperide)		
	LANTUS Breakfast	LANTUS Dinner	LANTUS Bedtime	LANTUS Breakfast	LANTUS Bedtime	NPH Bedtime
Number of subjects treated*	112	124	128	234	226	227
HbA _{1c}						
Baseline mean	7.56	7.53	7.61	9.13	9.07	9.09
Endstudy mean	7.39	7.42	7.57	7.87	8.12	8.27
Mean change from baseline	-0.17	-0.11	-0.04	-1.26	-0.95	-0.83
Basal insulin dose (IU)						
Endstudy mean	27.3	24.6	22.8	40.4	38.5	36.8
Mean change from baseline	5.0	1.8	1.5			
Total insulin dose (IU)				NA**	NA	NA
Endstudy mean	53.3	54.7	51.5			
Mean change from baseline	1.6	3.0	2.3			

*Intent to treat **Not applicable

INDICATIONS AND USAGE

LANTUS is indicated for once-daily subcutaneous administration for the treatment of adult and pediatric patients with type 1 diabetes mellitus or adult patients with type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

CONTRAINDICATIONS

LANTUS is contraindicated in patients hypersensitive to insulin glargine or the excipients.

WARNINGS

Hypoglycemia is the most common adverse effect of insulin, including LANTUS. As with all insulins, the timing of hypoglycemia may differ among various insulin formulations. Glucose monitoring is recommended for all patients with diabetes.

Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, timing of dosing, manufacturer, type (e.g., regular, NPH, or insulin analogs), species (animal, human), or method of manufacture (recombinant DNA versus animal-source insulin) may result in the need for a change in dosage. Concomitant oral antidiabetes treatment may need to be adjusted.

PRECAUTIONS

General:

LANTUS is not intended for intravenous administration. The prolonged duration of activity of insulin glargine is dependent on injection into subcutaneous tissue. Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia.

LANTUS must NOT be diluted or mixed with any other insulin or solution. If LANTUS is diluted or mixed, the solution may become cloudy, and the pharmacokinetic/pharmacodynamic profile (e.g., onset of action, time to peak effect) of LANTUS and/or the mixed insulin may be altered in an unpredictable manner. When LANTUS and regular human insulin were mixed immediately before injection in dogs, a delayed onset of action and time to maximum effect for regular human insulin was observed. The total bioavailability of the mixture was also slightly decreased compared to separate injections of LANTUS and regular human insulin. The relevance of these observations in dogs to humans is not known.

As with all insulin preparations, the time course of LANTUS action may vary in different individuals or at different times in the same individual and the rate of absorption is dependent on blood supply, temperature, and physical activity.

Insulin may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Hypoglycemia:

As with all insulin preparations, hypoglycemic reactions may be associated with the administration of LANTUS. Hypoglycemia is the most common adverse effect of insulins. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as long duration of diabetes, diabetes nerve disease, use of medications such as beta-blockers, or intensified diabetes control (see PRECAUTIONS, Drug Interactions). Such situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to patients' awareness of hypoglycemia.

The time of occurrence of hypoglycemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen or timing of dosing is changed. Patients being switched from twice daily NPH insulin to once-daily LANTUS should have their initial LANTUS dose reduced by 20% from the previous total daily NPH dose to reduce the risk of hypoglycemia (see DOSAGE AND ADMINISTRATION, Changeover to LANTUS).

The prolonged effect of subcutaneous LANTUS may delay recovery from hypoglycemia.

In a clinical study, symptoms of hypoglycemia or counterregulatory hormone responses were similar after intravenous insulin glargine and regular human insulin both in healthy subjects and patients with type 1 diabetes.

Renal Impairment:

Although studies have not been performed in patients with diabetes and renal impairment, LANTUS requirements may be diminished because of reduced insulin metabolism, similar to observations found with other insulins (see CLINICAL PHARMACOLOGY, Special Populations).

Hepatic Impairment:

Although studies have not been performed in patients with diabetes and hepatic impairment, LANTUS requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism, similar to observations found with other insulins (see CLINICAL PHARMACOLOGY, Special Populations).

Injection Site and Allergic Reactions:

As with any insulin therapy, lipodystrophy may occur at the injection site and delay insulin absorption. Other injection site reactions with insulin therapy include redness, pain, itching, hives, swelling, and inflammation. Continuous rotation of the injection site within a given area may help to reduce or prevent these reactions. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Reports of injection site pain were more frequent with LANTUS than NPH human insulin (2.7% insulin glargine versus 0.7% NPH). The reports of pain at the injection site were usually mild and did not result in discontinuation of therapy.

Immediate-type allergic reactions are rare. Such reactions to insulin (including insulin glargine) or the excipients may, for example, be associated with generalized skin reactions, angioedema, bronchospasm, hypotension, or shock and may be life threatening.

Intercurrent Conditions:

Insulin requirements may be altered during intercurrent conditions such as illness, emotional disturbances, or stress.

Information for Patients:

LANTUS must only be used if the solution is clear and colorless with no particles visible (see DOSAGE AND ADMINISTRATION, Preparation and Handling).

Patients must be advised that LANTUS must NOT be diluted or mixed with any other insulin or solution. (See PRECAUTIONS, General.)

Patients should be instructed on self-management procedures including glucose monitoring, proper injection technique, and hypoglycemia and hyperglycemia management. Patients must be instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate or skipped insulin dose, inadvertent administration of an increased insulin dose, inadequate food intake, or skipped meals. Refer patients to the LANTUS Information for the Patient circular for additional information.

As with all patients who have diabetes, the ability to concentrate and/or react may be impaired as a result of hypoglycemia or hyperglycemia.

Patients with diabetes should be advised to inform their health care professional if they are pregnant or are contemplating pregnancy.

Drug Interactions:

A number of substances affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

The following are examples of substances that may increase the blood-glucose-lowering effect and susceptibility to hypoglycemia: oral antidiabetes products, ACE inhibitors, disopyramide, fibrates, fluoxetine, MAO inhibitors, propoxyphene, salicylates, somatostatin analog (e.g., octreotide), sulfonamide antibiotics.

The following are examples of substances that may reduce the blood-glucose-lowering effect of insulin: corticosteroids, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives).

Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

In mice and rats, standard two-year carcinogenicity studies with insulin glargine were performed at doses up to 0.455 mg/kg, which is for the rat approximately 10 times and for the mouse approximately 5 times the recommended human subcutaneous starting dose of 10 IU (0.008 mg/kg/day), based on mg/m². The findings in female mice were not conclusive due to excessive mortality in all dose groups during the study. Histiocytomas were found at injection sites in male rats (statistically significant) and male mice (not statistically

significant) in acid vehicle containing groups. These tumors were not found in female animals, in saline control, or insulin comparator groups using a different vehicle. The relevance of these findings to humans is unknown.

Insulin glargine was not mutagenic in tests for detection of gene mutations in bacteria and mammalian cells (Ames- and HGPRT-test) and in tests for detection of chromosomal aberrations (cytogenetics in vitro in V79 cells and in vivo in Chinese hamsters).

In a combined fertility and prenatal and postnatal study in male and female rats at subcutaneous doses up to 0.36 mg/kg/day, which is approximately 7 times the recommended human subcutaneous starting dose of 10 IU (0.008 mg/kg/day), based on mg/m², maternal toxicity due to dose-dependent hypoglycemia, including some deaths, was observed. Consequently, a reduction of the rearing rate occurred in the high-dose group only. Similar effects were observed with NPH human insulin.

Pregnancy:

Teratogenic Effects: Pregnancy Category C. Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. The drug was given to female rats before mating, during mating, and throughout pregnancy at doses up to 0.36 mg/kg/day, which is approximately 7 times the recommended human subcutaneous starting dose of 10 IU (0.008 mg/kg/day), based on mg/m². In rabbits, doses of 0.072 mg/kg/day, which is approximately 2 times the recommended human subcutaneous starting dose of 10 IU (0.008 mg/kg/day), based on mg/m², were administered during organogenesis. The effects of insulin glargine did not generally differ from those observed with regular human insulin in rats or rabbits. However, in rabbits, five fetuses from two litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development appeared normal.

There are no well-controlled clinical studies of the use of insulin glargine in pregnant women. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in such patients. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers:

It is unknown whether insulin glargine is excreted in significant amounts in human milk. Many drugs, including human insulin, are excreted in human milk. For this reason, caution should be exercised when LANTUS is administered to a nursing woman. Lactating women may require adjustments in insulin dose and diet.

Pediatric Use:

Safety and effectiveness of LANTUS have been established in the age group 6 to 15 years with type 1 diabetes.

Geriatric Use:

In controlled clinical studies comparing insulin glargine to NPH human insulin, 593 of 3890 patients with type 1 and type 2 diabetes were 65 years and older. The only difference in safety or effectiveness in this subpopulation compared to the entire study population was an expected higher incidence of cardiovascular events in both insulin glargine and NPH human insulin-treated patients.

In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly (see PRECAUTIONS, Hypoglycemia).

ADVERSE REACTIONS

The adverse events commonly associated with LANTUS include the following:

Body as a whole: allergic reactions (see PRECAUTIONS)

Skin and appendages: injection site reaction, lipodystrophy, pruritus, rash (see PRECAUTIONS)

Other: hypoglycemia (see WARNINGS and PRECAUTIONS)

In clinical studies in adult patients, there was a higher incidence of treatment-emergent injection site pain in LANTUS-treated patients (2.7%) compared to NPH insulin-treated patients (0.7%). The reports of pain at the injection site were usually mild and did not result in discontinuation of therapy. Other treatment-emergent injection site reactions occurred at similar incidences with both insulin glargine and NPH human insulin.

Retinopathy was evaluated in the clinical studies by means of retinal adverse events reported and fundus photography. The numbers of retinal adverse events reported for LANTUS and NPH treatment groups were similar for patients with type 1 and type 2 diabetes. Progression of retinopathy was investigated by fundus photography using a grading protocol derived from the Early Treatment Diabetic Retinopathy Study (ETDRS). In one clinical study involving patients with type 2 diabetes, a difference in the number of subjects with ≥ 3 -step progression in ETDRS scale over a 6-month period was noted by fundus photography (7.5% in LANTUS group versus 2.7% in NPH treated group). The overall relevance of this isolated finding cannot be determined due to the small number of patients involved, the short follow-up period, and the fact that this finding was not observed in other clinical studies.

OVERDOSAGE

An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and sometimes long-term and life-threatening hypoglycemia. Mild episodes of hypoglycemia can usually be treated with oral carbohydrates. Adjustments in drug dosage, meal patterns, or exercise may be needed.

More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid reoccurrence of hypoglycemia.

DOSAGE AND ADMINISTRATION

LANTUS is a recombinant human insulin analog. Its potency is approximately the same as human insulin. It exhibits a relatively constant glucose-lowering profile over 24 hours that permits once-daily dosing.

LANTUS may be administered at any time during the day. LANTUS should be administered subcutaneously once a day at the same time every day. For patients adjusting timing of dosing with LANTUS, see **WARNINGS** and **PRECAUTIONS, Hypoglycemia**. LANTUS is not intended for intravenous administration (see **PRECAUTIONS**). Intravenous administration of the usual subcutaneous dose could result in severe hypoglycemia. The desired blood glucose levels as well as the doses and timing of antidiabetes medications must be determined individually. Blood glucose monitoring is recommended for all patients with diabetes. The prolonged duration of activity of LANTUS is dependent on injection into subcutaneous space.

As with all insulins, injection sites within an injection area (abdomen, thigh, or deltoid) must be rotated from one injection to the next. In clinical studies, there was no relevant difference in insulin glargine absorption after abdominal, deltoid, or thigh subcutaneous administration. As for all insulins, the rate of absorption, and consequently the onset and duration of action, may be affected by exercise and other variables.

LANTUS is not the insulin of choice for the treatment of diabetes ketoacidosis. Intravenous short-acting insulin is the preferred treatment.

Pediatric Use:

LANTUS can be safely administered to pediatric patients ≥ 6 years of age. Administration to pediatric patients < 6 years has not been studied. Based on the results of a study in pediatric patients, the dose recommendation for changeover to LANTUS is the same as described for adults in **DOSAGE AND ADMINISTRATION, Changeover to LANTUS**.

Initiation of LANTUS Therapy:

In a clinical study with insulin naïve patients with type 2 diabetes already treated with oral antidiabetes drugs, LANTUS was started at an average dose of 10 IU once daily, and subsequently adjusted according to the patient's need to a total daily dose ranging from 2 to 100 IU.

Changeover to LANTUS:

If changing from a treatment regimen with an intermediate- or long-acting insulin to a regimen with LANTUS, the amount and timing of short-acting insulin or fast-acting insulin analog or the dose of any oral antidiabetes drug may need to be adjusted. In clinical studies, when patients were transferred from once-daily NPH human insulin or ultralente human insulin to once-daily LANTUS, the initial dose was usually not changed. However, when patients were transferred from twice-daily NPH human insulin to LANTUS once

daily, to reduce the risk of hypoglycemia, the initial dose (IU) was usually reduced by approximately 20% (compared to total daily IU of NPH human insulin) and then adjusted based on patient response (see PRECAUTIONS, Hypoglycemia).

A program of close metabolic monitoring under medical supervision is recommended during transfer and in the initial weeks thereafter. The amount and timing of short-acting insulin or fast-acting insulin analog may need to be adjusted. This is particularly true for patients with acquired antibodies to human insulin needing high-insulin doses and occurs with all insulin analogs. Dose adjustment of LANTUS and other insulins or oral antidiabetes drugs may be required; for example, if the patient's timing of dosing, weight, or lifestyle changes, or other circumstances arise that increase susceptibility to hypoglycemia or hyperglycemia (see PRECAUTIONS, Hypoglycemia).

The dose may also have to be adjusted during intercurrent illness (see PRECAUTIONS, Intercurrent Conditions).

Preparation and Handling:

Parenteral drug products should be inspected visually prior to administration whenever the solution and the container permit. LANTUS must only be used if the solution is clear and colorless with no particles visible.

The syringes must not contain any other medicinal product or residue.

Mixing and diluting. LANTUS must NOT be diluted or mixed with any other insulin or solution (see PRECAUTIONS, General).

HOW SUPPLIED

LANTUS 100 units per mL (U 100) is available in the following package size:
10 mL vials (NDC 0088-2220-33)

Storage:

Unopened Vial:

Unopened LANTUS vials should be stored in a refrigerator, 36°F - 46°F (2°C - 8°C). LANTUS should not be stored in the freezer and it should not be allowed to freeze. Discard vial if frozen.

Open (In Use) Vial:

Opened vials, whether or not refrigerated, must be used within 28 days. They must be discarded if not used within 28 days. If refrigeration is not possible, the open vial in use can be kept unrefrigerated for up to 28 days away from direct heat and light, as long as the temperature is not greater than 86°F (30°C).

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Manufactured by:

Aventis Pharma Deutschland GmbH

D-65926 Frankfurt am Main

Germany

Manufactured for:

Aventis Pharmaceuticals Inc.

Kansas City, MO 64137 USA

US Patents 5,656,722, 5,370,629, and 5,509,905

Made in Germany

LANTUS[®] **(insulin glargine [recombinant DNA origin] injection)**

Patient Information for the LANTUS 10 mL vial (1000 units per vial) 100 units per mL (U-100)

This leaflet tells you about LANTUS (LAN-tus) and about how to use LANTUS in a vial. At the end of the leaflet is a list of vocabulary words you may find useful. Read this information carefully before you use LANTUS. Read the information you get when you refill your LANTUS prescriptions because there may be new information. This leaflet does not take the place of complete discussions with your health care professional. If you have questions about LANTUS or about diabetes, talk with your health care professional.

What is the most important information I should know about LANTUS?

Do NOT dilute or mix LANTUS with any other insulin or solution. It will not work as intended, and you may lose blood sugar control, which could be serious.

What is LANTUS?

LANTUS is a long-acting synthetic (man-made) human insulin to treat diabetes. You need a prescription to get LANTUS. Always be sure the pharmacy gives you the right insulin. The carton and vial should look like the ones in this picture.



Diabetes is a disease caused when the body cannot produce or use insulin. Insulin is a hormone produced by the pancreas. Your body needs insulin to turn glucose (sugar) from food into energy. If your body does not make enough insulin, you need another source of insulin so you will not have too much sugar in your blood. That is why you must take insulin injections.

LANTUS is similar to the insulin made by your body. It is used once a day to lower blood glucose. Like other insulins, you take LANTUS by injecting it in the fatty layer under the skin (subcutaneously). The dose your health care professional prescribes helps keep the glucose level in your blood close to normal.

You will be able to tell if LANTUS is working by testing your blood and/or urine for glucose.

LANTUS contains active and inactive ingredients. The active ingredient is insulin. It is dissolved in a colorless sterile (germ-free) fluid. The concentration is 100 units/mL (U-100). Inactive ingredients are zinc, glycerol, m-cresol, and water for injection.

Insulin injections play an important role in keeping your diabetes in control. But the way you live – your diet, careful monitoring of your glucose levels, exercise, and planned physical activity – all work with your insulin to help you control your diabetes.

Who should NOT take LANTUS?

You should not take LANTUS if you are allergic to insulin or any of the inactive ingredients in LANTUS.

What sort of syringe should I use?

Always use a syringe that is marked for U-100 insulin preparations. If you use the wrong syringe, you may get the wrong dose and develop a blood glucose level that is too low or too high.

Use disposable syringes and needles only once. Throw them away properly. Use a new needle and syringe every time you dose. **Never** share needles and syringes.

How do I draw the insulin into the syringe?

Do NOT dilute or mix LANTUS with any other insulin or solution. The syringe must not contain any other medicine or residue.

Follow these steps:

1. Wash your hands.
2. Check the insulin to make sure it is clear and colorless. Do not use it if it is cloudy or if you see particles.
3. If you are using a new vial, remove the protective cap. **Do not** remove the stopper.
4. Wipe the top of the vial with an alcohol swab.
5. Draw air into the syringe equal to your insulin dose. Put the needle through the rubber top of the vial and push the plunger to inject the air into the vial.
6. Leave the syringe in the vial and turn both upside down. Hold the syringe and vial firmly in one hand.
7. Make sure the tip of the needle is in the insulin. With your free hand, pull the plunger to withdraw the correct dose into the syringe.
8. Before you take the needle out of the vial, check the syringe for air bubbles. If bubbles are in the syringe, hold the syringe straight up and tap the side of the syringe until the bubbles float to the top. Push the bubbles out with the plunger and draw insulin back in until you have the correct dose.
9. Remove the needle from the vial. Do not let the needle touch anything. You are now ready to inject.

How do I inject LANTUS?

Inject LANTUS under your skin once a day. You may take LANTUS at any time during the day but you must take it at the same time every day.

You do not need to shake the vial before use. You should look at the medicine in the vial. If the medicine is cloudy or has particles in it, throw the vial away and get a new one. Check the expiration date.

Do NOT mix or dilute LANTUS with any other insulin or solution or LANTUS will not work as intended, and you may lose blood sugar control, which could be serious.

Follow these steps:

1. Decide on an injection area - either upper arm, thigh or abdomen. Injection sites within an injection area must be different from one injection to the next.
2. Use alcohol to clean the skin where you are going to inject.
3. Pinch the skin. Stick the needle in the way your doctor, nurse, or diabetes educator showed you. Release the skin
4. Slowly push in the plunger of the syringe all the way, making sure you have injected all the insulin. Leave the needle in the skin for several seconds.
5. Pull the needle straight out and gently press on the spot where you injected yourself for several seconds. **Do not rub the area.**
6. Follow your health care professional's instructions for throwing away the needle and syringe. Used needles and syringe should be placed in sharps containers (such as red biohazard containers), hard plastic containers (such as detergent bottles), or metal containers (such as an empty coffee can). Such containers should be sealed and disposed of properly.

If your blood glucose reading is high or low, tell your health care professional so the dose can be adjusted.

What can affect how much insulin I need?

Illness. Illness may change how much insulin you need. It is a good idea to think ahead and make a "sick day" plan with your health care professional so you will be ready when this happens. Be sure to test your blood and urine often and call your health care professional if you are sick.

Pregnancy and nursing. The effects of LANTUS on an unborn child or on a nursing baby are unknown, therefore, tell your health care professional if you plan to become pregnant or breast feed, or if you become pregnant. You may need to use another medicine. Your diabetes may be harder to control when you are pregnant. It is important for you to monitor your glucose closer than usual during this time.

Medicines. Other medicines, including non-prescription medicines, and dietary supplements can change the way insulin works. Therefore, tell your health care professional about all other medicines and supplements you are taking. Do not change your medicine doses yourself.

For example, your body may need more insulin if you take birth control, thyroid, decongestant, or diet pills. Your body may need less insulin if you are taking antidepressants, antidiabetes pills, or ACE inhibitors (used to lower blood pressure, for certain heart conditions and kidney disease).

Exercise. Exercise may change the way your body uses insulin. Be sure to check with your health care professional before you start an exercise program.

Travel. If you travel across time zones, talk with your health care professional about how to time your injections. When you travel, wear your medical alert identification. Take extra insulin and supplies with you.

What if I want to drink alcohol?

Before you drink alcohol, talk to your health care professional about its effect on diabetes.

What are the possible side effects of insulins?

1. Hypoglycemia (low blood sugar):

Hypoglycemia is often called an "insulin reaction" or "low blood sugar." It may occur when you do not have enough glucose in your blood.

Early warning signs of hypoglycemia may be different or less noticeable in some people. That is why it is important to check your glucose as you have been advised by your health care professional.

Hypoglycemia can occur with:

- **The wrong insulin dose.** This can happen when too much insulin is injected.
- **Medicines that directly lower glucose or increase sensitivity to insulin.** This can happen with oral (taken by mouth) antidiabetes drugs, sulfa antibiotics (for infections), ACE inhibitors (used to lower blood pressure, for certain heart conditions and kidney disease), salicylates including aspirin, some antidepressants, and with other medicines.
- **Medical conditions that limit the body's glucose reserve, lengthen the time insulin stays in the body, or that increase sensitivity to insulin.** These conditions include diseases of the adrenal glands, the pituitary, the thyroid gland, the liver, and the kidney.
- **Not enough carbohydrate (sugar or starch) intake.** This can happen if a meal or snack is missed or delayed, you have vomiting or diarrhea that decreases the amount of glucose absorbed by your body or you have consumed alcohol as it interferes with carbohydrate metabolism

- **Too much glucose use by the body.** This can happen if you exercise too much or have higher than normal metabolism rates due to fever.
- **Poor injection technique**

Hypoglycemia can be mild or severe. Its onset may be rapid. Patients with very good (tight) glucose control, patients with diabetes neuropathy (nerve problems), or patients using some beta-blockers (used for high blood pressure and heart conditions) may have few warning symptoms before severe hypoglycemia develops.

Hypoglycemia may reduce your ability to drive a car or use mechanical equipment without risk of injury to yourself or others. Severe hypoglycemia can cause temporary or permanent harm to your heart or brain. **It may cause unconsciousness, seizures, or death.** Symptoms of hypoglycemia include:

- anxiety, irritability, restlessness, trouble concentrating, personality changes, mood changes, or other abnormal behavior
- tingling in your hands, feet, lips, or tongue
- dizziness, light-headedness, or drowsiness
- nightmares or trouble sleeping
- headache
- blurred vision or slurred speech
- palpitations (rapid heart beat)
- sweating
- tremor (shaking) or unsteady gait (walking)

. If you have frequent or severe hypoglycemia or if you have trouble recognizing the symptoms of hypoglycemia, talk to your health care professional.

Mild to moderate hypoglycemia can be treated by eating or drinking carbohydrates (fruit juice, raisins, sugar candies, milk or glucose tablets).

More severe or continuing hypoglycemia may require the help of another person or emergency medical personnel. Someone with hypoglycemia who cannot take sugar by mouth needs medical help fast and will need treatment with a glucagon injection or glucose given intravenously. Without immediate medical help, serious reactions or even death could occur.

Talk with your health care professional about severe, continuing, or frequent hypoglycemia, and hypoglycemia for which you had few warning symptoms.

2. Hyperglycemia (high blood sugar):

Hyperglycemia occurs when you have too much glucose in your blood. Usually, it means there is not enough insulin to break down the food you eat into energy your body can use. Hyperglycemia can be caused by a fever, an infection, stress, eating more than you should, taking less insulin or antidiabetes agents than prescribed, or it can be part of the natural progression of diabetes.

Hyperglycemia can occur with:

- **The wrong insulin dose.** This can happen from injecting too little or no insulin, or the insulin's ability to lower glucose is changed by incorrect storage (freezing, excessive heat), or usage after the expiration date.
- **Too much carbohydrate intake.** This can happen if you eat larger meals, eat more often or increase the proportion of carbohydrate in your meals
- **Medicines that directly increase glucose or decrease sensitivity to insulin.** This can happen, for example, with thiazides (water pills), corticosteroids, or birth control pills.
- **Medical conditions that increase the body's production of glucose or decrease sensitivity to insulin.** These medical conditions include fevers, infections, heart attacks, and stress.
- **Poor injection technique**

Routine testing of your blood will let you know if you have hyperglycemia. If your tests are often high, tell your health care professional so your dose of medicine can be changed.

Hyperglycemia can be mild or severe. It can **progress to diabetic ketoacidosis (DKA), very high glucose levels or hyperosmolar coma and result in unconsciousness and death.**

Diabetic ketoacidosis occurs most often in patients with Type 1 diabetes but it can occur in patients with type 2 diabetes who become seriously ill.

Because some patients experience few symptoms of hyperglycemia and ketosis, it is important to monitor your glucose regularly.

Symptoms of hyperglycemia or DKA include:

- confusion or drowsiness
- fruity smelling breath
- rapid, deep breathing
- increased thirst
- decreased appetite, nausea, or vomiting
- abdominal (stomach area) pain
- rapid heart rate
- increased urination and dehydration (too little fluid in your body)

More severe or continuing hyperglycemia or DKA requires prompt evaluation and treatment by your health care professional. Do not use LANTUS to treat diabetic ketoacidosis.

3. Allergic reactions:

In rare cases, a patient may be allergic to an insulin product. Severe insulin allergies may be life-threatening. If you think you are having an allergic reaction, get medical help right away. Signs of insulin allergy are:

- a rash all over your body
- shortness of breath
- wheezing (trouble breathing)
- a fast pulse
- sweating
- low blood pressure

4. Possible reactions on the skin at the injection site:

Injecting insulin can cause the following reactions on the skin at the injection site:

- a little depression in the skin (lipoatrophy)
- skin thickening (lipohypertrophy)
- red, swelling, itchy skin (injection site reaction)

An injection site reaction should clear up in a few days or a few weeks. If it does not go away and it continues to occur, tell your health care professional.

You can reduce the chance of getting lipoatrophy and lipohypertrophy if you change the injection site each time. Tell your health care professional if you have these problems. You may need to learn to inject your insulin a different way.

How should I store LANTUS?

Unopened Vials:

Store new unopened LANTUS vials in the refrigerator (not the freezer) between 36°F - 46°F (2°C - 8°C). Do not freeze LANTUS. If a vial freezes, throw it away. Keep LANTUS out of direct heat and light

Open (In Use) vial:

Once a vial is opened, you can keep it in the refrigerator or as cool as possible (below 86°F [30°C]), but the opened 10 mL vial must be used within 28 days. If refrigeration is not possible, the open vial in use can be kept unrefrigerated for up to 28 days away from direct heat and light, as long as the temperature is not greater than 86°F (30°C). For example, do not leave it in your car on a summer day.

Do not use a vial of LANTUS after the expiration date stamped on the label

VOCABULARY

Glucose – A form of sugar that the body uses for fuel. It is made when food is broken down in the digestive system. Blood carries glucose to the cells.

Hyperglycemia – Too much glucose in the blood. Usually testing, not symptoms, reveals a too-high level.

Hypoglycemia – Also called insulin reaction. It means that glucose levels in the blood are too low.

Insulin – A hormone that helps the cells in your body use glucose.

Ketoacidosis (kee-toe-as-ih-DOE-sis) – A dangerous condition caused when the body does not have enough insulin.

LANTUS – A long-acting insulin similar to insulin made by your body. It is used once a day to lower blood glucose.

Lipoatrophy (LIP-o-AT-troe-fee) – Loss of fat under the skin. Can be caused by repeated insulin injections in the same place.

Lipohypertrophy (LIP-o-hi-PER-troe-fee) – A lump under the skin caused by an overgrowth of fat cells. Can be caused by repeated insulin injections in the same place.

Pancreas (PAN-kree-as) – A gland near the stomach that produces insulin.

Subcutaneous (sub-ku-TAE-nee-us) – The fatty layer under the skin.

ADDITIONAL INFORMATION

DIABETES FORECAST is a national magazine designed especially for patients with diabetes and their families and is available by subscription from the American Diabetes Association, National Service Center, 1701 N. Beauregard Street, Alexandria, Virginia 22311, 1-800-DIABETES (1-800-342-2383).

Another publication, **DIABETES COUNTDOWN**, is available from the Juvenile Diabetes Research Foundation International (JDRF), 120 Wall Street, 19th Floor, New York, New York 10005, 1-800-JDF-CURE (1-800-533-2873). You may also visit the JDRF website at www.jdf.org.

To get more information about diabetes, check with your health care professional or diabetes educator or visit www.DiabetesWatch.com. To get more information about LANTUS, ask your health care professional or call 1-800-633-1610.

Rev. xxxx

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